REMARKS

Claim Amendments

Claims 1-5 are pending and under consideration. As described below, claims 1-5 have been amended to clarify that the objects of the invention are combinations of separate nucleic acids and related methods and kits utilizing the claimed combinations of nucleic acids. No new matter has been added as a result of these amendments.

35 U.S.C. §112, Second Paragraph Rejections

Claims 1 and 3-4 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention. Specifically, the Examiner rejects claim 3 for "failing to recite a final process step that clearly relates back to the claim preamble, and over the recitation of the term 'a target sequence' and 'the target sequence' for the reasons set forth in the prior Office Action" (See the Office Action, page 2). Applicants respectfully traverse this rejection.

Applicants have amended claim 3 to recite "the target sequence" in step (a) in accordance with the Examiner's suggestion. Applicants thank the Examiner for her helpful suggestion. In view of this amendment, Applicants submit that this rejection is now moot and should be withdrawn.

The Examiner also rejects claims 1 and 3-4 as being indefinite in view of the phrase "A composition of matter consisting of SEQ ID NO. 2 and SEQ ID NO. 3" in claim 1. According to the Examiner, it is not clear whether this language encompasses two different nucleic acid molecules or a single molecule consisting of SEQ ID NO. 2 and SEQ ID NO. 3. Applicants respectfully traverse this rejection.

Applicants have amended claim 1 to more clearly recite the present invention. Specifically, in its amended form, claim 1 recites a combination of nucleic acids that comprise two separate nucleic acid molecules having the nucleotide sequences of SEQ ID NO. 2 and SEQ ID NO. 3 respectively. Therefore, in view of this amendment to claim 1, Applicants submit that this rejection is now moot and should be withdrawn.

35 U.S.C. §112, First Paragraph Rejection

Claims 1 and 3-4 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The Examiner takes the position that the claims contain "subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the claimed invention." The Examiner states that while the specification discloses amplification primers consisting of SEQ ID NO. 2 and SEQ ID NO. 3, the specification does not disclose any molecules consisting of only these two particular sequences. Applicants respectfully traverse this rejection.

As discussed above, Applicants have amended claim 1 to recite a combination of nucleic acids that comprise a first nucleic acid that has a nucleotide sequence of SEQ ID NO. 2 and a second nucleic acid that has a nucleotide sequence of SEQ ID NO. 3. The specification clearly provides support for combinations comprising two nucleic acids having the nucleotide sequences of SEQ ID NO. 2 and SEQ ID NO. 3 respectively (See, for example, page 4, lines 11-14 and page 9, lines 31-35).

Therefore, in view of the amendment to claim 1, Applicants believe that this rejection is now moot and should be withdrawn.

35 U.S.C. §102(b) Rejection

In the Office Action, the Examiner withdrew her previous rejection under 35 U.S.C. §102(b) in view of Applicants' amendment to claim 1 reciting a composition "consisting of" SEQ ID NO. 2 and SEQ ID NO. 3. Because in this Amendment Applicants have amended claim 1 to again recite the transition "comprising" rather than "consisting of," Applicants would like to address the §102(b) rejection previously made by the Examiner so that this rejection it is not reinstated.

The Examiner previously rejected claim 1 as being anticipated under 35 U.S.C. §102(b) in view of Drazen et al (WO 98/39477). Drazen et al teach, *inter alia*, the human ß2-adrenergic receptor gene. While it is true that the ß2-adrenergic receptor gene comprises both SEQ ID NO. 2 and SEQ ID NO. 3, Drazen et al. do not teach first and second nucleic acids that have the specific nucleotide sequences recited in SEQ ID NOS. 2 and 3 as claimed in amended claim 1. Therefore, Applicants respectfully submit that Drazen et al. do not anticipate any of the currently pending claims 1-5.

35 U.S.C §103 Rejection

The Examiner rejects claims 1-5 as being obvious over Dewar et al. in view of Drazen et al. and Matalon et al. (U.S. Patent No. 5,679,635) for the reasons set forth in the Office Action mailed on October 11, 2000.

The Examiner reads Dewar et al. to teach a method for the specific detection of codon 16 and codon 27 polymorphisms in the human ß2 adrenergic receptor gene. As the Examiner correctly explains, in Dewar et al.'s method, primers are used to amplify a region of the gene encompassing both polymorphisms. The polymorphisms are then detected by hybridization of amplification products with allele specific probes. As the Examiner recognizes, Dewar et al. do not teach or suggest primers comprising or consisting of SEQ ID

NOs. 2 or 3 or allele specific probes comprising or consisting of SEQ ID NOs. 4 or 5.

The Examiner points out that Drazen et al. teach the sequence of the human ß2-adrenergic receptor gene and further teach a variant gene comprising the codon 16 polymorphism discussed by Dewar et al. The Examiner states that SEQ ID NO. 2 targets a site approximately 50 nucleotides downstream from the Dewar et al.'s forward primer, and that SEQ ID NO. 3 targets a site approximately 80 nucleotides upstream from Dewar et al.'s reverse primer. It is also true that SEQ ID NOs. 4 and 5 overlap, but are not identical to, Dewar et al.'s allele specific probes. Drazen et al. teach that detection of the codon 16 polymorphism alone may be used to assess risk for adverse response to chronic ß-agonist administration.

The Examiner further reasons that a skilled artisan would have been motivated to modify Dewar et al.'s method to a detect codon 16 polymorphism alone (as opposed to both the codon 16 and codon 27 mutations) since it would require amplification of a shorter segment of the ß2 gene and, therefore, would require less time and fewer reagents (See the Office Action, page 5). However, the Examiner also admits that Applicants' primers and probes are neither taught nor suggested in Dewar et al.'s method (See the Office Action, pages 4-5). Nevertheless, the Examiner takes a position that design, selection, and production of suitable probes and primers for use in PCR and allele specific hybridization is routine in the art (See the Office Action, pages 5-6). To support her argument, the Examiner cites Matalon et al. (U.S. Patent No. 5,679,635). Matalon et al. states that the "design and selection of suitable probes and primers is routine for the skilled worker" (See column 14, lines 26-27). Therefore, the Examiner combines the teachings of Dewar et al., Drazen et al., and Matalon et al. to find Applicants' claims obvious absent a showing of unexpected results. Applicants respectfully traverse this rejection.

Applicants respectfully disagree with the Examiner's position and her reliance on Matalon et al. to establish obviousness. First, Matalon et al. do not disclose or teach anything regarding the human ß2-adrenergic receptor gene. Instead, Matalon et al. teach primers and probes that are useful for detecting mutations in the aspartoacylase gene. Second, it does not appear to Applicants that Matalon et al. teach or provide any "unexpected" results for their claimed primers and probes. Thereupon, in view of this, it is unfair for the Examiner to require Applicants to provide "unexpected" results for Applicants' novel and unobvious claimed primers and probes which are directed to a completely different gene and nucleic acid polymorphisms associated therewith than those disclosed by Matalon et al. Third, Applicants contend that Matalon et al. is incorrect in stating that the design and selection of suitable probes and primers is routine. In fact, as will be discussed in more detail below, all primer and probe sequences do not function identically, and therefore, selecting effective primers that would hybridize to a known target is not obvious.

Applicants submit that primer and probe sequences can be initially selected based on comparisons between known sequences to find conserved regions. However, even when conserved sequences are selected, they do not necessarily work in an amplification reaction. In practice, many primer and probe sequences must be tested in an amplification reaction setting to determine the suitability of the primer or probe sequences for their intended purpose. For example, efficiency of detection is often dependent on the distance between the primers. Specifically, if the primers are too close, a lot of product is obtained which cannot be detected over background (i.e., primer dimers), or there is not enough room for the probe to bind. On the other hand, if the primers are too far from each other, one may obtain little or no product. Additionally, the efficiency of the hybridization is also dependent on the degree of sequence identity between the primer and the target and the reaction condition used (in particular, the annealing or hybridization temperature).

Because there is some variability in the genomic sequences of various ß2 adrenergic receptor isolates, not all primers will detect all targets equally or predictably. If there is a poor match between the primers or probes, one would have to run reactions at various annealing temperatures until the product is detected or include additives to the reaction buffer that improve annealing between mismatched primers and targets. These steps are not at all obvious and require inventive skill. Accordingly, all possible primer and probe sequences are not functionally equivalent and a commercially acceptable efficiency of any primer or probe sequences cannot be predicted with any certainty.

Furthermore, Applicants draw the Examiner's attention to He Q. et al. *Biotechniques*, 17(1): 82-86 (1994), a copy of which is enclosed. This reference details the unexplained difficulties surrounding the selection of primer and probe sequences and indicates that adjusting reaction parameters is not necessarily a means for making primer or probe sequences efficacious. In fact, the reference suggests choosing different primer or probe sequences instead of trying to get an unresponsive set of primers to work by changing reaction conditions. Hence, all primer and probe sequences are not functionally equivalent and selecting alternative primer or probe sequences that can be employed for their intended purpose requires inventive skill and is not obvious.

In conclusion, Applicants' primers and probes are not taught in the prior art and it would not have been obvious to a person of ordinary skill in the art how to obtain the claimed primers and probes. Accordingly, in view of the above arguments, Applicants submit this rejection is now moot and should be withdrawn.

Double Patenting Rejection

The Examiner rejects claims 1, 3, and 5 under the doctrine of obviousness-type double patenting as being unpatentable over claims 4-7 of U.S. Patent 6,593,092.

In response to this rejection, Applicants herewith enclose a terminal disclaimer in accordance with 37 CFR §1.321. In view of the submission of this terminal disclaimer, Applicants submit that this rejection is now moot and should be withdrawn.

CONCLUSION

Applicants respectfully submit that the claims comply with the requirements of 35 U.S.C. Sections 112 and 103. Accordingly, a Notice of Allowance is believed in order and is respectfully requested.

Should the Examiner have any questions concerning the above, she is respectfully requested to contact the undersigned at the telephone number listed below. If the Examiner notes any further matters which the Examiner believes may be expedited by a telephone interview, the Examiner is requested to contact the undersigned.

If any additional fees are incurred as a result of the filing of this paper, authorization is given to charge deposit account no. 23-0785.

Respectfully submitted,

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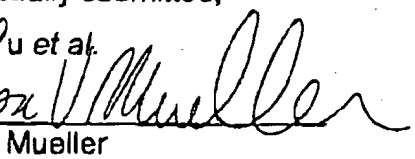

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